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[Intervention Review]

Ivermectin for onchocercal eye disease (river blindness)

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ABSTRACT

Background

It is believed that ivermectin (a microfilaricide) could prevent blindness due to onchocerciasis. However, when given to everyone in communities where onchocerciasis is common, the effects of ivermectin on lesions affecting the eye are uncertain and data on whether the drug prevents visual loss are unclear.

Objectives

The aim of this review was to assess the effectiveness of ivermectin in preventing visual impairment and visual field loss in onchocercal eye disease. The secondary aim was to assess the effects of ivermectin on lesions affecting the eye in onchocerciasis.

Search methods

We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (*The Cochrane Library* 2012, Issue 3), MEDLINE (January 1950 to April 2012), EMBASE (January 1980 to April 2012), the metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictip/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 2 April 2012.

Selection criteria

We included randomised controlled trials with at least one year of follow-up comparing ivermectin with placebo or no treatment. Participants in the trials were people normally resident in endemic onchocercal communities with or without one or more characteristic signs of ocular onchocerciasis.

Data collection and analysis

Two review authors independently extracted data and assessed trial quality. We contacted study authors for additional information. As trials varied in design and setting, we were unable to perform a meta-analysis.

Main results

The review included four trials: two small studies (n = 398) in which people with onchocercal infection were given one dose of ivermectin or placebo and followed up for one year; and two larger community-based studies (n = 4941) whereby all individuals in selected communities were treated every six or 12 months with ivermectin or placebo, whether or not they were infected, and followed for two to three years. The studies provide evidence that treating people who have onchocerciasis with ivermectin reduces the number of microfilariae in their skin and eye(s) and reduces the number of punctate opacities. There was weaker evidence that ivermectin reduced the risk of chorioretinitis. The studies were too small and of too short a duration to provide evidence for an effect on sclerosing keratitis, iridocyclitis, optic nerve

disease or visual loss. One community-based study in communities mesoendemic for the savannah strain of *O.volvulus* provided evidence that annual mass treatment with ivermectin reduces the risk of new cases of optic nerve disease and visual field loss. The other community-based study of mass biannual treatment of ivermectin in communities affected by the forest strain of *O.volvulus* demonstrated reductions in microfilarial load, punctate keratitis and iridocyclitis but not sclerosing keratitis, chorioretinitis, optic atrophy or visual impairment. The study was underpowered to estimate the effect of ivermectin on visual impairment and other less frequent clinical signs. The studies included in this review reported some adverse effects, in particular an increased risk of postural hypotension in people treated with ivermectin.

Authors' conclusions

The lack of evidence for prevention of visual impairment and blindness should not be interpreted to mean that ivermectin is not effective, however, clearly this is a key question that remains unanswered. The main evidence for a protective effect of mass treatment with ivermectin on visual field loss and optic nerve disease comes from communities mesoendemic for the savannah strain of *O.volvulus*. Whether these findings can be applied to communities with different endemicity and affected by the forest strain is unclear. Serious adverse effects were rarely reported. None of the studies, however, were conducted in areas where people are infected with *Loa loa* (loiasis).

PLAIN LANGUAGE SUMMARY

Ivermectin for river blindness (onchocerciasis)

Onchocerciasis is caused by tiny worms and is transmitted from person to person by a small biting fly. The fly breeds in fast flowing rivers and streams mainly in West Africa. The disease causes severe itching and thickening of the skin and damages structures at the front and back of the eye. It also affects the nerve that connects the eye with the brain.

Four studies based in west Africa were included in the review; two small studies in Ghana and Liberia and two larger community-based ones in Nigeria and Sierra-Leone. In the smaller studies, people with onchocercal infection were given one dose of ivermectin or placebo and followed up for one year. In the larger studies all individuals in selected communities were treated every six or 12 months with ivermectin or placebo, whether or not they were infected, and followed for two to three years. This review found that ivermectin can prevent damage to the front of the eye but its effectiveness in preventing blindness remains uncertain.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Ivermectin to prevent and treat onchocercal eye disease in people infected with *O.volvulus*

ivermectin to prevent and treat onchocercal eye disease in people infected with *O.volvulus*

Patient or population: people infected with *O.volvulus*

Settings: community

Intervention: ivermectin

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	ivermectin				
Visual impairment Follow-up: 12 months	See comment	See comment	Not estimable	354 (2 studies)	See comment	No events seen in either treatment or control groups
Visual field loss Follow-up: 12 months	See comment	See comment	Not estimable	0 (0)	See comment	Not reported
Punctate keratitis Follow-up: 12 months	See comment	See comment	Not estimable	0 (2 studies)	See comment	Data could not be pooled however both studies reported significant reduction in number of punctate opacities
Sclerosing keratitis Follow-up: 12 months	222 per 1000	13 per 1000 (0 to 273)	RR 0.06 (0 to 1.23)	39 (1 study)	⊕⊕⊕⊖ low 1,2	
Iridocyclitis Follow-up: 12 months	See comment	See comment	Not estimable	0 (2 studies)	See comment	Data not pooled. See footnote for more details. ³
Chorioretinitis Follow-up: 12 months	146 per 1000	3 per 1000 (0 to 47)	RR 0.02 (0 to 0.32)	200 (1 study)	⊕⊕⊕⊖ moderate ⁴	
Optic nerve disease Follow-up: 12 months	See comment	See comment	Not estimable	354 (2 studies)	See comment	No events seen in either treatment or control groups

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Serious indirectness: Only one trial reported this finding on a subset of people with severe ocular onchocerciasis

² Serious imprecision: One small study (total participants 39): wide confidence intervals including 1.

³ [Dadzie 1989](#): 7/116 in ivermectin group and 0/38 placebo group had mild iridocyclitis that resolved by 3 months after treatment and left no sequelae. [Taylor 1988](#) "no ivermectin-treated patients had uveitis at the three year examination". (NOTE: placebo group given ivermectin at 12 months)

⁴ Serious indirectness: Actual outcome reported was new or progression of retinal pigment epithelium atrophy which is an early manifestation of chorioretinal change.

Summary of findings 2. Ivermectin to prevent and treat onchocercal eye disease in people living in communities affected by *O. volvulus*

ivermectin to prevent and treat onchocercal eye disease in people living in communities affected by *O. volvulus*

Patient or population: people living in communities affected by *O. volvulus*

Settings: community

Intervention: ivermectin

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	ivermectin				
Visual impairment Follow-up: 24 months	22 per 1000	24 per 1000 (7 to 77)	RR 1.08 (0.33 to 3.5)	485 (1 study)	⊕⊕⊕⊕ very low ^{1,2,3}	
Visual field loss Follow-up: mean 24 months	180 per 1000	108 per 1000 (74 to 160)	RR 0.60 (0.41 to 0.89)	636 (1 study)	⊕⊕⊕⊕ high	
Punctate keratitis Follow-up: 24 months	285 per 1000	94 per 1000 (63 to 140)	RR 0.33 (0.22 to 0.49)	551 (1 study)	⊕⊕⊕⊕ moderate ¹	
Sclerosing keratitis Follow-up: 24 months	348 per 1000	258 per 1000 (181 to 369)	RR 0.74 (0.52 to 1.06)	560 (1 study)	⊕⊕⊕⊕ low ^{1,3}	
Iridocyclitis Follow-up: 24 months	217 per 1000	135 per 1000 (93 to 195)	RR 0.62 (0.43 to 0.9)	554 (1 study)	⊕⊕⊕⊕	

					moderate ¹
Chorioretinitis Follow-up: 24 months	60 per 1000	105 per 1000 (55 to 202)	RR 1.75 (0.91 to 3.37)	528 (1 study)	⊕⊕○○ low ^{1,3}
Optic nerve disease Follow-up: 24 months	48 per 1000	37 per 1000 (27 to 51)	RR 0.78 (0.57 to 1.06)	3577 (2 studies)	⊕⊕○○ low ^{1,4}

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Serious limitations in design: participants and outcome assessors adequately masked but other aspects of trial design such as sequence generation, allocation concealment and incomplete outcome data not clearly reported.

² Serious indirectness: Some of the visual impairment reported may have been attributed to other causes of visual loss. .

³ Serious imprecision: wide confidence intervals include 1.

⁴ Serious inconsistency: $I^2 = 76\%$. [Abiose 1993](#) found beneficial effect of ivermectin on new cases of optic nerve disease (risk ratio 0.65, 95% CI 0.45 to 0.93) and [Whitworth 1991a](#) found no difference in optic atrophy between ivermectin and placebo groups at 24 months follow-up (risk ratio 1.40, 95% CI 0.73 to 2.68).

BACKGROUND

Description of the condition

Onchocerciasis is an insect-borne disease caused by the filaria nematode (*Onchocerca volvulus*). It is transmitted from person to person by black-flies (*Simulium* species). Onchocerciasis is also called river blindness because the black-fly vector breeds in fast-flowing rivers and transmission is generally limited to people who live or work near such rivers.

The infective worms enter the human body through the black-fly bite and develop into mature adult worms (macrofilariae). The adult worms mate and the adult female produces millions of baby worms (microfilariae) which migrate throughout the skin. The actual route of entry of microfilariae into the eye is not known but proposed routes include the sheaths of the posterior ciliary arteries and nerves (arteries and nerves supplying the eye), the blood circulation, the cerebrospinal fluid and along the orbital septum and the cheek ligaments. Microfilariae may be seen in the cornea (the transparent outer wall of the eye) or the anterior chamber (the space between the cornea and the iris) by the slit lamp (an optical microscope used for examining the eye). While alive, the microfilariae cause little or no inflammation or immune response. Onchocercal eye disease generally develops after a long exposure to onchocercal infection, although eye lesions may occur rapidly when the intensity of infection is high. Generally, eye lesions tend to appear in individuals between the age of 30 and 45 years and are usually more commonly seen in males who work outdoors.

The main pathological changes seen in the back of the eye appear to be related to the local invasion and death of the microfilariae within the retinal tissue (Burnham 1998). It is believed that the dead microfilariae precipitate a severe inflammatory reaction which leads to the characteristic lesions affecting the back of the eye associated with ocular morbidity and blindness (Winthrop 2011). Additional research has identified *Wolbachia*, a bacteria which lives symbiotically within the mature adults worms (Saint Andre 2002). The presence of the *Wolbachia* or microfilariae may be responsible for the inflammatory immune response in front of the eye which is associated with punctate keratitis (inflammatory changes seen in the cornea that appear as fluffy white opacities); sclerosing keratitis (severe inflammatory changes seen in the cornea associated with corneal scarring); and iridocyclitis (inflammatory changes seen in the iris) (Hise 2007; Saint Andre 2002).

The pathogenesis of the lesions affecting the back of the eye: chorioretinitis (inflammation of the choroid and the retina); and optic neuritis (inflammation of the optic nerve) with subsequent optic atrophy (loss of nerve fibres in the optic nerve) is less clear and somewhat controversial. An autoimmune pathogenesis has been proposed based on the observation of the structural similarity between an *onchocerca volvulus* antigen (Ov39) and a human retinal antigen (hr44) (Cooper 1996). This similarity may initiate the development of an autoimmune disease that has the potential to progress even in the absence of the organism. In other words, the chorioretinal pathology is initiated by the presence of local microfilariae, whereas the extension of the lesions does not require their presence (Cooper 1997). This would explain why the decrease in ocular microfilarial loads following ivermectin treatment reported in some trials does not interrupt the pathological process in the retina which probably was initiated early in life (i.e. before the age of 15 years) (Chippaux 1999).

This raises the question of whether treatment with ivermectin can be expected to prevent progressive posterior segment disease or indeed long-term blindness from this cause. The main pathways to blindness due to onchocerciasis are sclerosing keratitis, chorioretinitis and optic nerve disease, although blindness can result from lesions that affect different parts of the eye i.e. iridocyclitis leading to secondary cataract (opacity of the lens within the eye) or secondary glaucoma (increase in pressure within the eye).

Onchocerciasis is endemic in 34 countries; 26 in the African region, six in the region of the Americas and two in the Eastern Mediterranean (Johnson 1998). As a public health problem the disease is most closely associated with Africa, where it constitutes a serious obstacle to socio-economic development. Recent estimates indicate that about 18 million people globally are infected of whom 99% are in Africa (WHO 2000). A further 120 million people world-wide are at risk of developing the disease, 96% of whom are in Africa (WHO 2000).

Onchocerciasis causes severe skin disease but the main public health importance of the disease is blindness. Of the 18 million people infected with the disease an estimated 270,000 are blind and 500,000 severely visually disabled (Rolland 1974). The overall consequences of onchocerciasis can only be fully appreciated when uni-ocular blindness, visual impairment and constriction of the peripheral visual field are taken into consideration (Abiose 1994; Murdoch 1997).

Description of the intervention

Ivermectin (marketed as Mectizan), a microfilaricide, has been used for the treatment of parasites of domestic animals for many years. In 1982 ivermectin was tested in patients with onchocerciasis and was found to reduce significantly the microfilarial counts in skin snips of infected individuals for a period of six months to one year (Aziz 1982). It has been suggested from dose-finding trials that 150 micrograms/kg body weight represents an optimal dose of ivermectin (White 1987). The exclusion criteria for ivermectin use include children less than five years; pregnant women; women breastfeeding within one month of giving birth and individuals with disorders of the central nervous system (such as epilepsy).

Clinical trials and subsequent field experience have shown that ivermectin is a rapidly effective, well-tolerated, single dose, microfilaricide which causes little or no Mazzotti reaction (severe inflammatory response) and is suitable for use in mass campaigns (Johnson 1998). Commonly reported adverse effects after ivermectin use are skin reactions including itching; musculoskeletal pains; fever; swelling of the face, joints and limbs; headaches and dizziness; lymphadenopathy; eye reactions and nodule pain. These are usually mild and self-limiting. Some individuals may develop a severe symptomatic postural hypotension (a sudden fall in blood pressure) which may require emergency facilities for resuscitation.

Concerns have been expressed recently over the potential for ivermectin to cause unconsciousness in treated individuals who have concomitant *Loa loa* infection (another kind of filarial worm infestation), with very high microfilaraemia. Gardon 1997 reported two cases of probable *Loa* encephalopathy after mass treatment of about 17,877 persons with ivermectin in the Lekie area of Cameroon, where onchocerciasis and loiasis are both endemic.

Consequently it has been proposed that, before launching mass ivermectin distribution programs, communities in which the intensity of concomitant *Loa loa* microfilaraemia are highly in need of being identified and monitoring strategies instituted before treatment begins (Boussinesq 1998).

Apart from its use in controlling onchocerciasis, it has been reported that ivermectin has a secondary effect of reducing intestinal helminths in humans. Whitworth 1991b showed that ivermectin had a significant effect on *Ascaris* (round worm) infection, reducing prevalence and intensity for at least three months. In a qualitative study in north-east Nigeria on community-perceived benefits of ivermectin treatment, worm expulsion was the most frequently stated benefit (Akogun 2000). Other perceived benefits were an increase in vitality, sexual drive and performance.

How the intervention might work

Although the exact pharmacological action of ivermectin is not well known, it is believed to exert its anti-parasitic action on microfilariae either by acting directly as a GABA-amino-butyric-acid (GABA) agonist or by causing an increase in tonic GABA release. It may therefore interfere with neural transmission causing paralysis of parasites (Aziz 1982). Apart from its microfilaricidal effects, ivermectin has also been observed to inhibit the release of microfilariae from the adult worm's uterus. The end result of these actions is a reduction in microfilarial loads in the body and eyes, prevention of progression of onchocercal lesions in the eye and skin and possibly prevention of blindness in the long term.

The control of onchocerciasis as a public health problem was achieved with the introduction of treatment with ivermectin annually or every six-months in endemic communities. However, there is some debate regarding the potential role of annual mass treatment with ivermectin in reducing transmission in endemic communities in order to achieve elimination to the extent at which treatment may be stopped (Abiose 2000; Richards 2000). It has been shown that distribution of ivermectin to 60% of the population results in a 70% to 75% post-treatment reduction in infected flies (Remme 1990). Similarly, mass treatment with ivermectin has been shown to be associated with a 94% reduction in the number of flies with developing infective larvae (Trpis 1990). Repeated annual treatment with ivermectin in Liberia was shown to reduce the incidence of new infections in untreated children by about 40% in the second year (Taylor 1990). Based on longitudinal research treatment over 15 to 17 years can interrupt transmission and reduce the expected number of new infections below levels postulated to achieve elimination (Diawara 2009; Tekle 2012). Even after treatment was stopped no new infections or transmission was detected after two years of follow-up (Diawara 2009). It is now believed that new infections and interruption of transmission can be achieved with treatment alone in endemic areas (Diawara 2009; Tekle 2012).

Whitworth 1992 Remme 1990

Why it is important to do this review

The control of onchocerciasis has been based at various times on large-scale nodulectomy, vector control or large-scale chemotherapy. The chemotherapeutic agents used prior to 1987 were suramin and diethylcarbamazine. While suramin was a good macrofilaricide (efficacious in killing the adult worms), it requires

intravenous injection and was found to be toxic to the kidneys. Diethylcarbamazine, a microfilaricide (efficacious in killing the baby worms), was associated with the development of the Mazzotti reaction, in which massive destruction and death of the baby worms stimulated a severe inflammatory response. This was shown to precipitate and accelerate the progression of optic nerve disease in individuals with a heavy onchocercal infection (Bird 1980).

The World Health Organization (WHO) has defined a new global strategy for controlling onchocerciasis that is based on yearly administration of single doses of ivermectin to affected populations (WHO 2000). Ivermectin is currently employed by the African Programme for Onchocerciasis Control (APOC) and the Onchocerciasis Elimination Programme for the Americas (OEPA) for mass treatment in hyper and mesoendemic communities. In 1987, Merck & Co., Inc. pledged to provide, at no cost, all the drugs necessary for as long as needed to overcome onchocerciasis as a public health problem. Between 1987 and the end of 1996, more than 65 million doses of ivermectin had been donated for distribution (WHO 2000).

Blindness remains the single most important public health problem posed by onchocerciasis. Although ivermectin has been shown to be an excellent microfilaricide, it is unclear how this translates to real benefits in terms of blindness prevention for those who suffer the disease. The microfilaricidal activity of ivermectin, no matter how great, is of only academic interest if a villager at risk of blindness from onchocerciasis cannot be told in clear terms how taking the drug reduces that risk. So far, evaluation of the effectiveness of ivermectin in preventing blindness has been based on surrogate measures such as the reduction of skin and ocular microfilarial loads, as well as possible improvement in anterior segment lesions (lesions affecting the front of the eye) such as punctate keratitis, sclerosing keratitis or iridocyclitis or some of the posterior segment lesions (lesions affecting the back of the eye) such as chorioretinitis or optic nerve disease. However, there are conflicting reports concerning the effects of ivermectin on these lesions as well as uncertainties about its effectiveness in preventing progressive visual loss especially from lesions affecting the back of the eye. This review, therefore, aimed to summarise systematically all the evidence from randomised controlled trials (RCTs) relating to the effectiveness of ivermectin in preventing progressive visual loss as well as its effects on onchocercal eye lesions in order to provide current best evidence on which to base decisions for practice and further research.

OBJECTIVES

The primary objective of this review was to assess the effectiveness of ivermectin on the prevention of visual loss in onchocercal ocular disease. A secondary objective was to assess the effects of ivermectin on onchocercal ocular lesions.

METHODS

Criteria for considering studies for this review

Types of studies

This review included RCTs. The unit of randomisation was either individuals or endemic onchocercal communities (cluster RCTs). Included trials were required to have at least a one-year follow-up.

Types of participants

Participants were people who were normally resident in a community that was endemic for onchocerciasis, with or without a positive skin snip for microfilariae or to have characteristic ocular signs of onchocerciasis. Participants could also be grouped as communities where the unit of randomisation was at the community level.

Types of interventions

We included RCTs comparing ivermectin treatment with placebo or no intervention. Treatment was defined according to the recommended dose of 150 micrograms ivermectin tablet per kg body weight, taken orally as a single dose semi-annually or annually.

Types of outcome measures

Primary outcomes

The primary outcomes for this review were as follows.

1. Visual acuity: the proportion of participants with new visual acuity loss (unilateral or bilateral) during the follow-up period.
2. Visual fields: the proportion of participants with new visual field deterioration (unilateral or bilateral) during the follow-up period.

Case definitions for primary outcome measures.

- New visual acuity loss: any case of visual impairment or blindness.
- New visual impairment: deterioration of visual acuity with best correction in either eye to less than 6/18 during the study period.
- New blindness: deterioration of visual acuity with best correction in either eye to less than 3/60 during the study period.
- Visual field deterioration: as defined by trial authors.

Secondary outcomes

The secondary outcomes for this review were as follows.

3. Parasitological - mean microfilariae count or proportion of participants with a microfilariae count more than one in:
 - a. cornea;
 - b. anterior chamber;
 - c. skin.
4. Clinical - new cases, progression or proportion of participants with:
 - a. punctate keratitis;
 - b. sclerosing keratitis;
 - c. iridocyclitis;
 - d. chorioretinitis;
 - e. optic nerve disease.
5. Adverse outcomes as reported in trials.

Secondary outcomes were as measured by the trial investigators and were considered according to the unit of randomisation in each study - either at the individual or community level.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2012, Issue 3, part of *The Cochrane Library*.

www.thecochranelibrary.com (accessed 2 April 2012), MEDLINE (January 1950 to April 2012), EMBASE (January 1980 to April 2012), the metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictip/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 2 April 2012.

See: Appendices for details of search strategies for CENTRAL (Appendix 1), MEDLINE (Appendix 2), EMBASE (Appendix 3), mRCT (Appendix 4), ClinicalTrials.gov (Appendix 5) and the ICTRP (Appendix 6).

Searching other resources

We searched the reference lists of identified trials to find additional trials. We used the Science Citation Index to find studies that had cited the identified trials. We contacted the investigators of the identified trials, Merck & Co., Inc. and practitioners who are active in the field (A Foster, UK; D Molyneux, UK; I Murdoch, UK) to identify additional published and unpublished studies. Attempts to contact Hans Remme of the WHO Onchocerciasis Control Project were unsuccessful.

Data collection and analysis

Selection of studies

Two review authors independently reviewed the titles and abstracts resulting from the searches. We obtained full copies of any report referring to possibly or definitely relevant trials. All full copies were assessed according to the [Criteria for considering studies for this review](#). Only trials meeting these criteria were assessed for methodological quality. Disagreements were resolved by discussion.

Data extraction and management

Two review authors extracted data using a form developed by the Cochrane Eyes and Vision Group and entered data into RevMan ([Review Manager 2011](#)). We resolved discrepancies by discussion. We combined data on the proportion of participants with early and advanced stages of the following lesions - keratitis, iridocyclitis, chorioretinitis and optic nerve disease. i.e. data on early and late keratitis were combined to give data on keratitis as an outcome. We combined data for the number of participants with a microfilariae count between one and four and those with a microfilariae count above four into the proportion of participants with a microfilariae count of more than one.

Assessment of risk of bias in included studies

For the first version of this review, we assessed trial quality according to methods set out in Section 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2005](#)). Four parameters were considered: allocation concealment; masking of participants and providers; masking of outcome assessment; and completeness of follow-up. Each parameter for trial quality was graded: A (adequate); B (unclear); C (inadequate). The a priori criterion for exclusion was that trials scoring C on allocation concealment were excluded. Two review authors independently assessed trial quality and disagreement was resolved by discussion. Review authors were not masked to the report authors and trial details during the assessment.

For the update in 2009 The Cochrane Collaboration's recommended tool for assessing risk of bias was used. This is a domain-based evaluation of allocation, blinding, incomplete outcome data and selective reporting. The 'Risk of bias' tables were completed by one review author (JE) and checked by another author (HE). For the 2012 update, the review authors' judgements within the 'Risk of bias' tables were labelled as: high; low; or unclear risk of bias as described in [Higgins 2011](#).

Measures of treatment effect

We calculated risk ratios for outcome measures reported as dichotomous data. We did not calculate summary measures for outcome measures reported as continuous data as neither standard deviations nor confidence intervals were reported.

Unit of analysis issues

We had anticipated that there would be cluster randomised trials available for this review, however, none were identified. All trials reported outcomes per person, not per eye.

Dealing with missing data

Our main analyses assume that missing data are missing at random. However, to see how reasonable this assumption might be we also performed sensitivity analyses with different assumptions about the missing data using methods as set out by White et al ([White 2008](#)). The "informative missingness odds ratio" (IMOR) refers to the ratio of the odds of the outcome among participants for whom data were missing and the odds of the outcome among participants who were observed. These IMORs can be assumed to be equal or different in the two trial arms. We performed four sensitivity analyses for selected outcomes. Firstly, we assumed the IMOR was 2 in treatment and control groups i.e. that people who were not seen were twice as likely to have the outcome. Secondly, we assumed that the IMOR was $\frac{1}{2}$ in both treatment and control groups i.e. that people who were not seen were half as likely to have the outcome. For the third and fourth sensitivity analyses, we assumed that the IMOR was opposite in treatment and control groups - i.e. 2 or $\frac{1}{2}$.

We carried out all analyses using the *metamiss* command in Stata (version 10.1, StataCorp LP, 4905 Lakeway Drive, College Station, TX 77845 USA).

Assessment of heterogeneity

We assessed heterogeneity by examining the forest plots and I^2 values.

Assessment of reporting biases

We planned to investigate publication bias by carrying out a scatter plot of the effect estimates from the individual studies

against their standard error. An asymmetric graph may indicate that smaller studies that are not statistically significant have not been published, although it also may indicate that the effects of treatment are different in small studies. Currently not enough trials are included in the analyses to assess publication bias.

We investigated selective outcome reporting by carrying out an "outcome matrix" and classifying missing outcomes according to the following classification (adapted from a list provided by Paula Williamson at a Cochrane training workshop on selective outcome reporting bias, Edinburgh March 2009).

- A: States outcome analysed but only reported the P value > 0.05 i.e. NS
- B: States outcome analysed but only reported that P value < 0.05
- C: Clear that outcome was analysed but insufficient data presented to be included in meta-analysis or full tabulation
- D: Clear that outcome was analysed but no results reported
- E: Clear that outcome was measured (for example, includes structurally related outcomes) but not necessarily analysed
- F: States that outcome was not measured
- G: Not mentioned but clinical judgement says likely to have been measured
- H: Not mentioned but clinical judgement says unlikely to have been measured
- I: Other give details

Data synthesis

Due to the variable methods used in trials for collecting and presenting outcome data, we considered pooling of results inappropriate.

Subgroup analysis and investigation of heterogeneity

Analyses of subgroups were not specified a priori and therefore we did not perform any in this review.

Sensitivity analysis

See '[Dealing with missing data](#)' section above.

RESULTS

Description of studies

Results of the search

The original electronic searches in February 2000 generated 347 citations and abstracts. These were screened and 92 full text articles were retrieved for further assessment. Five RCTs, reported in 10 articles, met the criteria for inclusion. Communication with Merck & Co., Inc, the manufacturers of Mectizan, and with experts in the field did not yield information on any further trials.

The following table summarises the updates:

Date	Number of new citations	Number of new studies for inclusion
February 2000	347	5 (subsequently revised to 4 as one report was of a subset of patients included in another trial)
December 2001	13	None

May 2005	173	None
December 2008	126	None
August 2009	33	None
April 2012	135	None

Included studies

Table 1 summarises the characteristics of the included studies.

Setting and participants

All four studies took place in west Africa: Liberia (Taylor 1988), northern Nigeria (Abiose 1993), northern Ghana (Dadzie 1989) and southern Sierra-Leone (Whitworth 1991a). All the studies recruited participants normally resident in endemic onchocercal communities.

Interventions

In all trials ivermectin was compared with placebo. The usual dose was 150 µg/kg body weight, however, Dadzie 1989 and Taylor 1988 had three treatment groups of 100,150 and 200 µg/kg. As the results of these groups were similar they have been pooled for the purposes of this review. Ivermectin was given as a single dose in Dadzie 1989 and Taylor 1988. In the community-based studies four annual (Abiose 1993) or biannual (Whitworth 1991a) doses were given.

Outcome measures

Assessment of outcome measures was by ocular or systemic examination. This included skin snip tests and visual field

examination in some cases. The assessments were undertaken by specialist doctors or specially trained eye nurses. Outcome measures were assessed and reported differently in the studies. For example, in Abiose 1993 visual field was assessed using the Friedmann Mark 1 Visual Field Analyser and visual field deterioration was defined as an absolute loss of at least 19 illuminated spots. In Taylor 1988 visual field was assessed using the clear dome perimeter with a 2 mm fibre-optic target, and visual field classified as either full, showing peripheral loss, loss to 20° of fixation, loss to 10° or loss to 5°. We have presented a descriptive report of the analyses of data from each of the four included trials.

For more detailed information on individual trials see 'Characteristics of included studies'.

Excluded studies

See 'Characteristics of excluded studies'.

Risk of bias in included studies

Figure 1 and Figure 2 summarise the assessment of the risk of bias in the included studies.

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

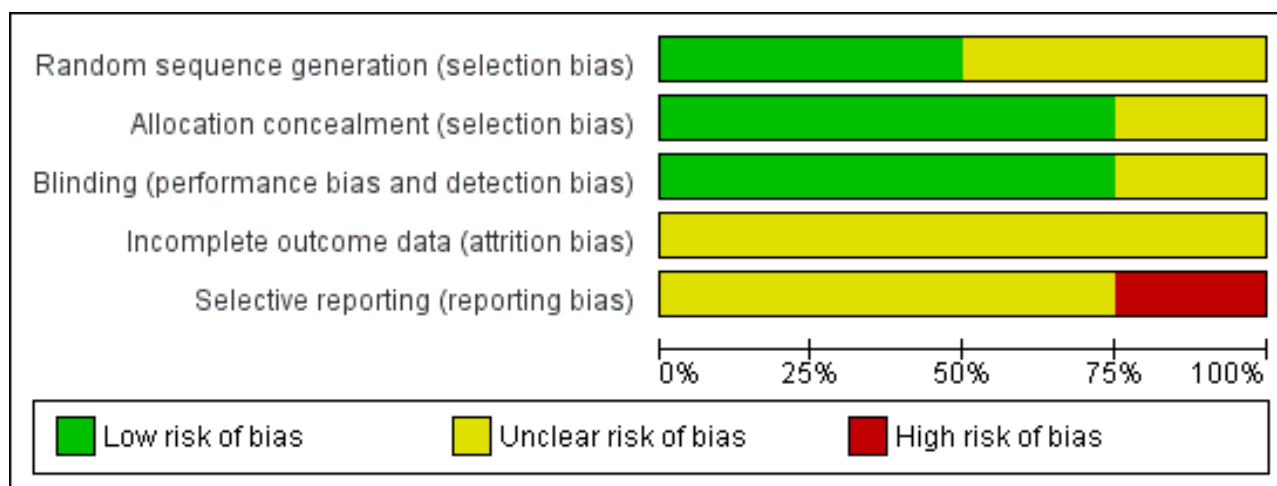


Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Abiose 1993	+	+	+	?	-
Dadzie 1989	?	+	?	?	?
Taylor 1988	+	+	+	?	?
Whitworth 1991a	?	?	+	?	?

Allocation

[Abiose 1993](#) was the only trial that reported adequate methods of sequence generation and allocation concealment. [Dadzie 1989](#) and [Taylor 1988](#) reported adequate methods of allocation concealment. For [Whitworth 1991a](#), methods for sequence generation and allocation concealment were not reported.

Blinding

All trials were placebo-controlled so we have assumed that participants and outcome assessors were adequately masked to treatment group.

Incomplete outcome data

[Table 2](#) shows the follow-up data for the included trials. Follow-up rates ranged from 73% ([Taylor 1988](#)) to 89% ([Whitworth 1991a](#)). However, the latter study only reported information from people who had received all four biannual doses of ivermectin or placebo. Losses to follow-up in the main trial were not given.

In [Abiose 1993](#) communities endemic for onchocerciasis were treated, that is everyone aged five years and above received ivermectin or placebo, however, children under the age of 15 years were not examined at follow-up. Although this means that not everyone treated was examined, it is hard to envisage that this would bias the resulting effect estimates as very few events would be expected in people aged five to 15 and there is no reason to suppose that the effect of ivermectin will be different in this age group.

Selective reporting

Data were reported rather sparsely for most outcomes. [Table 3](#) shows the outcome reporting grid. There is considerable potential for selective outcome reporting.

Effects of interventions

See: [Summary of findings for the main comparison Ivermectin to prevent and treat onchocercal eye disease in people infected with *O. volvulus*](#); [Summary of findings 2 Ivermectin to prevent and treat](#)

onchocercal eye disease in people living in communities affected by *O. volvulus*

Primary outcome measures

1. Visual acuity (visual impairment and blindness)

All four studies collected data on visual acuity.

Abiose 1993 did not report visual acuity outcome data.

Dadzie 1989 stated that 2% of participants showed deterioration in their visual acuity in the course of the follow-up examinations (12 months) without giving absolute figures for each treatment group. These differences were not statistically different between the four treatment groups.

Taylor 1988 observed 0/152 (0%) participants in the ivermectin groups and 1/48 (2.1%) participants in the placebo group developed visual acuity deterioration from 6/6 to 6/9 during the 12-month follow-up period. The definition of visual acuity deterioration used in the trial does not meet the definition used for this review. It does, however, imply that no participant developed visual impairment or blindness over the course of the study.

Whitworth 1991a reported explicitly data for the incidence of blindness and visual impairment. The definition used for blindness and visual impairment was consistent with the WHO guidelines. In this trial, six out of 255 people who were not visually impaired at baseline (2.4%) and who received four six-monthly doses of ivermectin developed visual impairment compared with 5/230 (2.3%) in the placebo group after four six-monthly doses of

ivermectin or placebo (risk ratio (RR) 1.08, 95% confidence interval (CI) 0.33 to 3.50).

2. Visual fields

Abiose 1993 reported the effect of ivermectin on visual field deterioration. Of the participants who were treated with at least one dose of ivermectin and completed a Friedmann field analysis at one or more of the follow-up examinations, 34/314 (10.8%) in the ivermectin group developed visual field deterioration compared with 58/322 (18%) in the placebo group (RR 0.60, 95% CI 0.41 to 0.89). We assessed the effects of missing data for this outcome (Table 4). There was little evidence that this effect could be attributed to the effects of missing data.

Dadzie 1989 collected data on visual field at baseline but did not report post-treatment visual field outcomes.

Taylor 1988 reported no case of further visual field deterioration during the period of follow-up (12 months) between the ivermectin and placebo groups.

Whitworth 1991a did not include visual field outcomes.

Secondary outcome measures

3. Parasitological

Abiose 1993 did not report parasitological outcomes.

Two trials (Dadzie 1989; Taylor 1988) reported parasitological outcome measures as continuous data (shown in the following table) but as they did not report standard deviations or confidence intervals we could not pool the data.

Outcome 12 months after one dose of ivermectin at baseline	Study	Ivermectin		Placebo	
		Geometric mean at baseline (before treatment)	Geometric mean at 12 months	Geometric mean at baseline (before treatment)	Geometric mean at 12 months
Number of microfilariae per mg skin	Taylor 1988	20.0	3.4	21	13
*Number of microfilariae in the anterior chamber	Dadzie 1989	6	0.2	4	1.3
	Taylor 1988	2.6	0.2	3.8	1.7
*Number of microfilariae in the cornea	Dadzie 1989	0.35	0	0.3	0.05
	Taylor 1988	0.4	0.15	0.65	0.7

*Approximate values as they are obtained from graphical output. Differences between ivermectin and placebo groups were reported to be statistically significant ($P < 0.05$).

Whitworth 1991a reported parasitological outcomes measured as categorical data.

Outcome after 4 doses of ivermectin at six-monthly intervals (2 years follow-up)	Ivermectin n/N	Placebo n/N	Risk ratio (95% confidence intervals)
Proportion with anterior chamber microfilarial count > 1	10/285	91/263	0.10 (0.05 to 0.19)

Proportion with corneal microfilarial count > 1	17/285	61/263	0.21 (0.12 to 0.37)
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4. Clinical

	Abiose 1993	Dadzie 1989	Taylor 1988	Whitworth 1991a
Outcome	n/N in ivermectin group, n/N in placebo group. One or more doses (max four) over 3 years. Mean duration of follow-up 2.54 years (range 1.41 to 3.25)		Figures are geometric means at baseline (before treatment) and 12 months after one dose of ivermectin	n/N in ivermectin group, n/N in placebo group at after 4 six-monthly doses of ivermectin i.e. 2 yrs follow-up risk ratio (RR) (95% confidence intervals)
Punctate keratitis	Not reported	"At one year all ivermectin treated groups showed a zero level whilst the placebo treated group was at 50% of the level before treatment"	Number of punctate opacities: baseline 0.8 (ivermectin) 1.2 (placebo): 12 months 0.1 (ivermectin) and 1.0 (placebo).	One or more punctate opacities 27/288 (ivermectin) and 75/263 (placebo) RR 0.33 (0.22 to 0.49)
Sclerosing keratitis	Not reported	Not reported	In a subsample of 39 participants with severe ocular onchocerciasis, there was a progression of sclerosing keratitis in 2/9 (22.2%) participants in the placebo group compared with 0/30 (0%) in the ivermectin group (OR 0.18, 95% CI 0.01 to 4.29).	83/293 (ivermectin) and 93/267 (placebo) RR 0.74 (0.52 to 1.06)
Iridocyclitis	Not reported	7/116 in ivermectin group and 0/38 placebo group had mild iridocyclitis that resolved by 3 months after treatment and left no sequelae.	"no ivermectin-treated patients had uveitis at the three year examination". (NOTE: placebo group given ivermectin at 12 months)	39/291 (ivermectin) and 57/263 (placebo) RR 0.62 (0.43 to 0.90)
Chorioretinitis	Not reported	"No new lesions were observed in the fundus of the eye."	New or progression of retinal pigment epithelium atrophy (an early manifestation of chorioretinal change) 0/152 (ivermectin) 7/48 (placebo) RR 0.02 (0.00 to 0.32)	Chorioretinitis 28/278 (ivermectin) 15/250 (placebo) RR 1.75 (0.91 to 3.37)
Optic nerve disease	New case of optic nerve disease: 45/1509 (ivermectin) 71/1536 (placebo): RR 0.65 (0.45 to 0.93)	"No retinal or optic nerve head changes were observed on fluorescein angiography of the patients who underwent this test"	"there were no new cases of optic neuritis or optic atrophy in any person in any treatment group throughout the study"	Optic atrophy: 22/281 (ivermectin) 14/251 (placebo) RR 1.40 (0.73 to 2.68)

5. Adverse drug reactions

Adverse reactions included cutaneous reactions, musculoskeletal reactions, fever, swelling of the face, joints and limbs, headaches and dizziness, lymphadenopathy, eye reactions and nodule pain. These reactions were either mild, moderate or severe.

[Abiose 1993](#) and [Taylor 1988](#) did not report adverse events.

In [Dadzie 1989](#), 8/116 (6.9%) participants in the ivermectin group compared with 0/38 (0%) in the placebo group reported severe symptomatic postural hypotension (RR 9, 95% CI 0.55 to 147.9).

In [Whitworth 1991a](#), 47/384 (12.2%) participants in the ivermectin group compared with 31/344 (9%) in the placebo group reported adverse drug effects of any kind (RR 1.36, 95% CI 0.88 to 2.09).

DISCUSSION

Summary of main results

This review includes the results of two different types of studies: two small studies in which people with onchocercal infection were given one dose of ivermectin or placebo and followed up for one year; and two larger community-based studies whereby all individuals in selected communities were treated every six or 12 months with ivermectin or placebo, whether or not they were infected, and followed for two to three years.

As the two types of studies are addressing two different questions we will consider them separately.

1. Ivermectin to prevent and treat onchocercal eye disease and its consequences in people infected with *O. volvulus*

See '[Summary of findings for the main comparison](#)'.

The results of [Dadzie 1989](#) and [Taylor 1988](#) provide evidence that treating people who have onchocerciasis with ivermectin reduces the number of microfilariae in their skin and eye (not shown in the 'Summary of findings' table) and reduces the number of punctate opacities. There was weaker evidence that ivermectin reduced the risk of chorioretinitis. There was no evidence for a protective effect for sclerosing keratitis, iridocyclitis, optic nerve disease or visual loss. However, the studies were too small and of too short a duration to provide evidence on these less frequent consequences of onchocercal infection.

2. Ivermectin to prevent and treat onchocercal eye disease in people living in communities affected by *O. volvulus*

See '[Summary of findings 2](#)'.

The results of one community-based study provides evidence that annual mass treatment with ivermectin reduces the risk of new cases of optic nerve disease and visual field loss in communities mesoendemic for the savannah strain of *O. volvulus* ([Abiose 1993](#)). The other community-based study, with mass biannual treatment of ivermectin in communities affected by the forest strain, demonstrated reductions in microfilarial load (not shown in the 'Summary of findings' table), punctate keratitis and iridocyclitis but not sclerosing keratitis, chorioretinitis, optic atrophy or visual impairment ([Whitworth 1991a](#)). However, this study was underpowered to estimate the effect of ivermectin on

visual impairment and other less frequent clinical signs. Only a small number of new cases of visual impairment developed over two years (11 cases in total, not all of which could be attributed to onchocerciasis).

Adverse effects

In [Whitworth 1991a](#), ivermectin was associated with a higher prevalence of adverse drug reactions compared with placebo, however, this was not statistically significant. [Dadzie 1989](#) showed a nine-fold increased risk of severe symptomatic postural hypotension in the ivermectin group but this was not statistically significant.

Overall completeness and applicability of evidence

With only four trials included in this review, the evidence for ivermectin in the treatment of onchocercal disease is incomplete. We can say with confidence that ivermectin reduces the microfilarial load and number of punctate opacities. However, the evidence for its effect on other signs of onchocercal eye disease, such as sclerosing keratitis, chorioretinitis and optic nerve disease is less certain. Most importantly, the effect of ivermectin in preventing visual loss, which is an outcome of primary importance to people suffering from river blindness, is unclear. The trials included in this systematic review were not primarily designed to evaluate the effectiveness of ivermectin in preventing onchocercal blindness and this outcome was not commonly reported. The lack of evidence for prevention of visual impairment and blindness should not be interpreted to mean that ivermectin does not have these effects, however, clearly this is a key question that remains unanswered.

Only two community-based trials are included in this review, one conducted in communities mesoendemic for the savannah strain in northern Nigeria and one in communities affected by the forest strain in Sierra-Leone. The Nigerian study demonstrated a protective effect of mass treatment with ivermectin on the incidence of optic nerve disease and visual field loss. However, it is unclear whether this finding applies to other communities with higher or lower infection rates and to communities affected by other strains of *O. volvulus*. Several reports suggest that onchocercal blindness is less common in forested areas compared with savannah areas, where blindness rates can reach 15% ([Burnham 1998](#); [Pond 1991](#); [Stevenson 1999](#); [WHO 1985](#)). It is believed that the savannah strain is more aggressive than the forest strain. These factors could influence the overall response of participants to the treatment being evaluated.

The studies included in this review reported some adverse effects, in particular an increased risk of postural hypotension in people treated with ivermectin. Unlike diethylcarbamazine, ivermectin does not rapidly eliminate microfilariae. This means that the Mazzotti reaction, which results from a massive overkill of numerous microfilariae all at once, is unlikely to be serious with ivermectin. However, none of the studies have been conducted in areas where people are infected with *Loa loa* (loiasis). Some studies have suggested that serious neurological adverse effects can occur when ivermectin is given to people with heavy infections of *Loa loa* ([Gardon 1997](#)).

Quality of the evidence

All the trials included in this review used a placebo-controlled group and therefore outcome assessment was graded as low risk of bias. The use of a placebo probably meant that sequence generation and allocation concealment were adequate as well but this was less well reported. Information on follow-up was less well reported and there may well be bias due to incomplete outcome data and selective outcome reporting.

A limitation of this review is the fact that all four trials included are published trials. It is possible that there are unpublished trials we did not identify. If trials with negative findings are more likely to remain unpublished (publication bias), the efficacy of ivermectin may be overestimated in this review. Visual examination of a funnel plot might have helped in determining the role of publication bias in this review. Multiple trials, which have reported a common outcome from which estimates of effects can be calculated, are needed in order to carry out a funnel plot. None of the reported outcomes in the four trials included in this review was uniformly reported in all the trials. Furthermore, the primary outcome measure for this review was explicitly reported in only one trial. Extensive efforts were made to contact pharmaceutical companies, trial authors and acknowledged experts in the area of onchocerciasis for unpublished trials of ivermectin for onchocerciasis in order to reduce the risk of publication bias. None was identified.

Potential biases in the review process

The review methods were revised for the update in 2009. This could have introduced bias if the choice of methods was influenced by knowledge of the results of the included trials. However, we think this is unlikely as the methods used are fairly standard. The conclusions of the review have not changed.

Agreements and disagreements with other studies or reviews

The lack of convincing evidence for the effectiveness of ivermectin in the prevention of onchocercal blindness was also noted by Abiose in a narrative overview of onchocercal ocular disease and the impact of ivermectin treatment (Abiose 1998). Abiose noted that 'in none of the studies was there any evidence of a reduction in the prevalence of blindness and a few new cases due to [onchocercal ocular disease] were observed. It may take a long time for the effect of Mectizan on the incidence of blindness to become apparent'.

Adverse effects have been noted in observational studies. In a review of eight uncontrolled community trials to determine the safety of ivermectin during large-scale treatment, De-Sole 1989 reported 49 cases of severe symptomatic postural hypotension among 50,929 persons treated from eight countries. This represents an incidence of approximately 0.1% over 72 hours. Chijioka 1992 reported two cases of severe symptomatic postural hypotension among 7556 people treated with ivermectin in south-east Nigeria. With the exception of rare serious reactions such as severe systematic postural hypotension, ivermectin is generally well tolerated (Goa 1991).

AUTHORS' CONCLUSIONS

Implications for practice

Some of the trials included in this review demonstrate that ivermectin may be effective in reducing punctate keratitis and iridocyclitis. However, its effectiveness in reducing chorioretinal lesions and preventing visual acuity loss in onchocercal eye disease remains unclear. The evidence for the effectiveness of ivermectin in the reduction of the incidence of onchocercal visual field loss and optic nerve disease reported in one trial with the savannah type strain should be applied with caution to hyperendemic onchocercal communities in which the forest type strain predominates.

As the benefits and harms of mass treatment with ivermectin are not well established, treatment programmes should monitor the effects of their programmes carefully.

Implications for research

The single most important public health problem posed by onchocerciasis is blindness and visual impairment. Future trials should not only focus on the microfilaricidal properties of ivermectin, but also consider its effects on posterior segment lesions, particularly chorioretinitis and its effectiveness in preventing visual acuity loss.

Given the widely held belief that ivermectin is the drug of choice for preventing and controlling blindness due to onchocerciasis, the present lack of suitable alternatives and ethical considerations may make it difficult for placebo-controlled randomised trials of ivermectin to be undertaken in the future. Scientists have intensified efforts on finding appropriate drugs which can kill the adult worms of onchocerciasis. Recently some eight anti-cancer compounds with potential macrofilaricidal properties have been identified (Kinnanom 2000). In addition, Dr Mark Taylor at the Liverpool School of Tropical Medicine has reported potential macrofilaricidal property of antibiotics of the tetracycline group. Certain species of bacteria (*Wolbachia*) are known to infect filarial worms; these probably play an important role in their fertility and contribute to the pathogenesis of filarial disease. Tetracycline antibiotics 'cure' the worms of their bacteria and in doing so affect the viability of the worms (Hoerauf 2001; Taylor 2000). Current studies are underway which are investigating the effects of moxidectin (NCT00790998) and doxycycline (ISRCTN95189962) relative to ivermectin.

Future trials should have appropriate sample sizes allowing sufficient power to detect important treatment differences with respect to preventing visual loss in onchocerciasis. The duration of these trials should be sufficiently long to be able to detect meaningful changes in visual acuity. Anticipating that these trials would be in rural communities, simple visual acuity tests such as the illiterate E chart could be used and outcome measures could be reported as 'proportion of participants in each treatment group becoming visually impaired or blind during follow-up' using the WHO definition. However, the visual acuity or visual field in the worse eye rather than the better eye should define an individual with visual impairment or blindness. This is to ensure that the real impact of onchocerciasis on blindness and visual impairment is not underestimated.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Abiose 1993

Methods	Method of allocation: individual randomisation with a blocked design. Sequential administration of pre-coded containers. Masking: participants, provider and outcome assessors masked.
Participants	Country: Northern Nigeria. Type of river blindness: savannah type. Number randomised: 8136*.

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Abiose 1993 (Continued)

Age: 5 years and above.

Sex: male and female.

Inclusion criteria: Individuals above 5 years normally resident in communities in which the prevalence of positive skin snip for microfilariae among residents 20 years and over was 30% or more.

Exclusion criteria: pregnant or lactating women; children < 5 years or weighing < 15 kg; Individuals with disorders of the central nervous system or other debilitating disease.

Number of participants analysed for incidence of optic nerve disease after exclusion of children < 15 years and individuals with optic nerve disease at baseline: 3045.

Interventions	Treatment: single dose ivermectin tablets taken orally and given annually for 3 years. Dose: 150 ug/kg. Control: placebo tablets taken orally and given once annually for 3 years. Duration of follow-up: 17 to 39 months.
Outcomes	Incidence of optic nerve disease, visual field deterioration.
Notes	Individuals who were 5 years or older were randomised but only individuals 15 years and above were re-examined for outcome measures and included for analyses.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation to the ivermectin or placebo group was done at the individual level with a blocked design." Abiose 1993 , page 131, first paragraph.
Allocation concealment (selection bias)	Low risk	"At registration a master card was completed for each individual. It carried identification information, including a photograph, a unique pre-printed identification number, and a pre-printed sequential treatment group number between 1 and 30. Merck, Sharp and Dohme donated 30 identical containers, numbered 1-30, to which ivermectin (6 mg per tablet) or a visually indistinguishable placebo tablet had been randomly allocated. Each participant received tablets from the container with the same number as his or her card. Staff conducting the trial were unaware which containers held ivermectin." Abiose 1993 , page 131, first paragraph.
Blinding (performance bias and detection bias) All outcomes	Low risk	See above
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"...3522 individuals examined at the first examination were re-examined at least once-an overall follow-up rate of 82%. The mean duration of follow-up for these individuals was 2-54 (range 1.41-3.25) years. There were no differences between the ivermectin and placebo groups in the mean duration of follow-up or in the proportions of participants re-examined at each examination." Abiose 1993 , page 131, results, first paragraph. Communities endemic for onchocerciasis were treated i.e. everyone aged 5 years and above received ivermectin or placebo. However, as very few people aged less than 15 years will experience significant onchocercal eye disease children under the age of 15 years were not examined at follow-up. Although this means that not everyone treated was examined, as this was an a priori decision at study design stage, and intervention/control groups were treated the same it is unlikely to have lead to any bias in estimating the effect of the intervention.
Selective reporting (reporting bias)	High risk	No information on pre-specified outcomes and only optic nerve disease and visual field loss reported.

Dadzie 1989

Methods	Method of allocation: individual randomisation with sequential administration of pre-packed, precoded envelopes which were labelled with allocation numbers. Masking:
Participants	Country: Northern Ghana. Type of river blindness: savannah type. Area under concomitant vector control. Number randomised: 198. Age: 15 to 64 years. Sex: male and female. Inclusion criteria: not available. Exclusion criteria: not available.
Interventions	Treatment: single dose ivermectin tablets taken orally and given annually. Dose: 100 ug/kg or 150 ug/kg or 200 ug/kg. Control: placebo tablet given as single dose. Duration of follow-up: 1 year.
Outcomes	Systemic reactions to treatment; Visual function: improvement or deterioration; Skin microfilariae load (geometric mean); Cornea, anterior chamber microfilarial load (geometric mean)**; Punctate opacity load; Sclerosing keratitis; Iridocyclitis; Fundus changes.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	"The doses of ivermectin or placebo were formulated as identical capsules and presented in pre-packed, precoded envelopes, each containing five capsules, and labelled with weight ranges and allocation numbers. On admission into hospital, the patients were given the allocation numbers sequentially and the contents of the envelopes with three weight ranges into which their body weights fitted. This procedure generated four groups of patients: the first with 49 patients who took 100 mcg/kg; the second with 50 patients who had 150 mcg/kg, the third with 50 patients who received 200 mcg/kg body weight of ivermectin and fourth with 49 patients who were given placebo consisting of 185 mg corn starch (STA-RX L500)." Dadzie 1989 , page 356.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	See above for allocation concealment which would also suggest that blinding was adequate. However, "The code of the study was broken after the month 6 review" Dadzie 1989 , page 356. The significance of this for subsequent examinations (at 12 months) is unclear.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"Only 154 of the 198 patients who were ophthalmologically examined on all occasions were considered in the analysis of the results.
Selective reporting (reporting bias)	Unclear risk	See Table 3

Taylor 1988

Methods	Method of allocation: Individual randomisation using computer generated random numbers. Drug administered in coded packages. Masking: provider, participants and outcome assessors masked.
Participants	Country: Grand Bassa County - Liberia. Type of river blindness: forest type. Number randomised: 200. Age: 12 to 60 years. Sex: male and female. Inclusion criteria: heavy skin microfilarial count greater than 15 microfilariae/mg skin. Exclusion criteria: pregnant and lactating women; people who had received anti-filaricidal drug within 1 year.
Interventions	Treatment: single dose ivermectin tablets taken orally and given annually. Dose: 100 ug/kg or 150 ug/kg or 200 ug/kg. Control: placebo tablet given as single dose. Duration of follow-up: 1 year.
Outcomes	Visual acuity; Visual field; Skin, cornea, anterior chamber microfilarial count (geometric mean)**; Punctate opacity load (geometric mean)**; Ocular reaction index; Sclerosing keratitis; Anterior uveitis; Retinal pigment epithelial atrophy; Optic nerve changes.
Notes	Number analysed in treatment groups not reported, therefore number randomised to treatment groups used for analyses.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Subjects were randomly assigned by using computer-generated random numbers to receive 100, 150, or 200 µg/kg of ivermectin/kg or placebo" White et al 1987, page 464, treatment protocol, first paragraph
Allocation concealment (selection bias)	Low risk	"The drug was provided in coded packages containing five identical capsules; each patient was treated individually and closely observed to ensure compliance." Newland 1988, page 562, treatment protocol, first paragraph Also see below for "blinding".
Blinding (performance bias and detection bias) All outcomes	Low risk	"Data were gathered in a double-masked fashion and entered for computer analysis prior to breaking the treatment code at six months. The patients were examined at 12 months without reference to the treatment code." Newland 1988, page 562, treatment protocol, first paragraph
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information on follow-up given.
Selective reporting (reporting bias)	Unclear risk	See Table 3

Whitworth 1991a

Methods	Method of allocation: individual randomisation with a blocked design. Computer generated random numbers. Concealed allocation using coded containers. Masking: provider, participants and outcome assessors masked.
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Ivermectin for onchocercal eye disease (river blindness) (Review)

Whitworth 1991a (Continued)

Participants	Country: Southern Sierra-Leone. Type of river blindness: forest type. Number randomised: 1625. Age: 1 year and above. Sex: male and female. Inclusion criteria: individuals normally resident in the study villages. Exclusion criteria (after randomisation): children under five years; pregnant and one month postpartum women; those with neurological disease including epilepsy; individuals with severe intercurrent infection.
Interventions	Treatment: single dose ivermectin tablets taken orally and given 6 monthly. Dose: 150 ug/kg body weight. Control: placebo tablet given 6 monthly. Duration of follow-up: 2 years.
Outcomes	Incidence of blindness; Incidence of visual impairment; Skin microfilarial load (mf/mg) (geometric mean)**; Prevalence of microfilariae in cornea, anterior chamber; Prevalence of punctate keratitis, sclerosing keratitis, iritis, Chorioretinitis, retinal pigment epithelial atrophy, adverse drug reactions.
Notes	Adverse reactions reported include: cutaneous reactions; musculoskeletal reactions; fever; swellings of the face, joints or limbs; headache; dizziness; lymphadenopathy; eye reactions; nodule pain.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"All inhabitants of 6 study villages in southern Sierra-Leone were allocated at random to receive either ivermectin (150µg/kg) or placebo throughout the trial." <i>Whitworth et al Transactions of the Royal Society of Tropical Medicine and Hygiene 1991, page 501 materials and methods.</i>
Allocation concealment (selection bias)	Unclear risk	Control group received placebo but no information about allocation and how it was concealed.
Blinding (performance bias and detection bias) All outcomes	Low risk	The control group received placebo and even though there was no information about allocation and how it was concealed we have assumed that people were unaware to which group they had been allocated.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The eye study aimed to examine 312 people who had received four doses of placebo and 331 who had received four doses of ivermectin. 272 (87%) of the placebo cohort and 296 (89%) of the ivermectin cohort were examined. However original numbers treated were much higher ranging from 812 to 870 in the ivermectin group and 813 to 875 in the placebo group.
Selective reporting (reporting bias)	Unclear risk	Unclear see Table 3

* Number randomised to treatment or placebo not clearly specified. The value given is the number of individuals initially registered and randomised.

** Standard deviation not reported therefore RevMan analysis for these outcome measures not possible.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Gardon 2002	All groups received ivermectin. No placebo group.

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ADDITIONAL TABLES

Table 1. Characteristics of included studies

Study	Location	Type of <i>O.volvulus</i> in locality	Characteristics of participants			Intervention	
			Total number randomised	Mean age (range)	% onchocercal infection	Ivermectin	Placebo
Abiose 1993*	Nigeria	savannah	4298	(15 to ?)	49% (age 5+) 72% (age 20+)	Approx 150 µg/kg Four doses over three years	Four doses over three years
Dadzie 1989	Ghana	savannah	198	32.5 (12 to 55)	100%	100, 150 and 200 µg/kg One dose	185 mg corn starch (STA-RX L500) One dose
Taylor 1988**	Liberia	forest	200	29.8 (12 to 60)	100%	100, 150 and 200 µg/kg One dose	One dose
Whitworth 1991a	Sier-ra-Leone	forest	643 people who had received 4 doses ivermectin or placebo	Estimated from grouped data at 41 years (5 to ?).	73%	150 µg/kg at 0,6,12,18 months. Everyone received ivermectin at 24 months.	0,6,12,18 months. All ivermectin at 24 months.

*Everyone aged 5 years and above was treated with ivermectin or placebo, however, only people aged 15 years and above were examined as part of the trial.

**800 people screened; of which 200 people with highest skin microfilarial counts were given ivermectin or placebo.

Table 2. Follow-up

Study	Follow-up	Ivermectin			Placebo		
		Number randomised	Number seen	% seen	Number randomised	Number seen	% seen
Abiose 1993*	Mean duration of follow-up 2.54 years (range 1.41 to 3.25)	?	1750	82	?	1772	82
Dadzie 1989**	3, 6 and 12 months	149	116	77.9	49	38	77.9
Taylor 1988	3, 6 and 12 months	152	111	73.0	48	31	64.6

Table 2. Follow-up (Continued)

Whitworth 1991a***	24 months	331	296	89.4	312	272	87.2
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*The trialists aimed to dose all trial participants aged 5 years or more with either ivermectin or placebo once a year for three years. 5021 individuals were registered in the trial and aged 15 years and older. Of these, 3522 (82%) were re-examined at least once during the course of the trial. "There were no differences between the ivermectin and placebo groups in the mean duration of follow-up or in the proportions of participants re-examined at each examination."

** Data reported (number seen) for participants who had data for all three examinations.

*** From a larger study of 1745 people, 643 (331 ivermectin; 312 placebo) people who had received 4 doses of either ivermectin or placebo were selected for the eye study.

Table 3. Outcome reporting grid

Outcome	Type	Abiose 1993	Dadzie 1989	Taylor 1988	Whitworth 1991a
Visual acuity	Continuous	E	A	E	E
Visual acuity: % with new visual impairment (< 6/18)	Dichotomous	E	E	✓	✓
Visual acuity: % with new blindness (< 3/60)	Dichotomous	✓	E	✓	E
Visual field: % with deterioration	Dichotomous	✓	H	✓	F
Microfilariae in skin	Continuous	E	B	C	H (stated measured pretreatment)
Microfilariae in skin	Dichotomous / Categorical	E	A	E	H (stated measured pretreatment)
Microfilariae in cornea	Continuous	E	B	C	E
Microfilariae in cornea	Dichotomous / Categorical	E	E	E	✓
Microfilariae in anterior chamber	Continuous	E	B	C	E
Microfilariae in anterior chamber	Dichotomous / Categorical	E	E	E	✓
Punctate keratitis % new cases	Dichotomous	E	B	D (geometric mean punctate corneal opacities reported)	✓
Sclerosing keratitis % new cases	Dichotomous	E	H	E	✓
Iridocyclitis % new cases	Dichotomous	E	✓	E	✓
Chorioretinitis % new cases	Dichotomous	E	✓	✓	✓
Optic nerve disease % new cases	Dichotomous	✓	✓	✓	✓
Adverse outcomes	Dichotomous	E	✓(pos- tural hy- poten- sion)	B (Mazot- ti reac- tion)	✓
Outcomes not prespecified in the review					
Improvement in visual acuity 2+ lines	Dichotomous	E	A	E	E
Deterioration in visual acuity 2+ lines	Dichotomous	E	A	E	E

Table 3. Outcome reporting grid (Continued)

Glaucoma	Dichotomous	E	E	E	Reported
Proportion visually impaired or blind at end of study	Dichotomous	E	E	E	Reported

Adapted from list provided by Paula Williamson at a Cochrane training workshop on selective outcome reporting bias, Edinburgh March 2009.

✓ Data included in the review

A: States outcome analysed but only reported the P value > 0.05 i.e. NS

B: States outcome analysed but only reported that P value < 0.05

C: Clear that outcome was analysed but insufficient data presented to be included in meta-analysis or full tabulation

D: Clear that outcome was analysed but no results reported

E: Clear that outcome was measured (for example, includes structurally related outcomes) but not necessarily analysed

F: States that outcome was not measured

G: Not mentioned but clinical judgement says likely to have been measured

H: Not mentioned but clinical judgement says unlikely to have been measured

I: Other give details

Table 4. Effect of missing data

Outcome: visual field loss		
Assumption regarding missing data	Risk ratio	95% confidence interval
Missing at random (available case analysis)	0.60	0.41 to 0.89
Odds outcome in non-observed twice that in observed in ivermectin and control groups	0.61	0.42 to 0.90
Odds outcome in non-observed half that in observed in ivermectin and control groups	0.60	0.40 to 0.89
Odds outcome in non-observed twice that in observed in ivermectin and half in control groups	0.75	0.51 to 1.11
Odds outcome in non-observed twice that in observed in ivermectin and half in control groups	0.49	0.33 to 0.72

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor Onchocerciasis

#2 MeSH descriptor Onchocerca

#3 MeSH descriptor Microfilaria

#4 onchocerc* or oncocerc*

#5 river near blindness

#6 (#1 OR #2 OR #3 OR #4 OR #5)

#7 MeSH descriptor Ivermectin

#8 ivermectin*

#9 mectizan*

#10 ivomec*

#11 MeSH descriptor Albendazole

#12 albendazole*

#13 MeSH descriptor Levamisole

#14 levamisole*

#15 (#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14)

#16 (#6 AND #15)

Appendix 2. MEDLINE (OVID) search strategy

1. randomized controlled trial.pt.
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. exp animals/
10. exp humans/
11. 9 not (9 and 10)
12. 8 not 11
13. exp onchocerciasis/
14. exp onchocerca/
15. microfilaria/
16. (onchocerc\$ or oncocerc\$).tw.
17. (river adj2 blindness).tw.
18. or/13-17
19. ivermectin/
20. ivermectin\$.tw.
21. mectizan\$.tw.
22. ivomec\$.tw.
23. albendazole/
24. albendazole\$.tw.
25. levamisole/
26. levamisole\$.tw.
27. or/19-26
28. 18 and 27
29. 12 and 28

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville et al ([Glanville 2006](#)).

Appendix 3. EMBASE (OVID) search strategy

1. exp randomized controlled trial/
2. exp randomization/
3. exp double blind procedure/
4. exp single blind procedure/
5. random\$.tw.
6. or/1-5
7. (animal or animal experiment).sh.
8. human.sh.
9. 7 and 8
10. 7 not 9
11. 6 not 10
12. exp clinical trial/
13. (clin\$ adj3 trial\$).tw.
14. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj3 (blind\$ or mask\$)).tw.
15. exp placebo/
16. placebo\$.tw.
17. random\$.tw.
18. exp experimental design/
19. exp crossover procedure/
20. exp control group/
21. exp latin square design/
22. or/12-21
23. 22 not 10

24. 23 not 11
 25. exp comparative study/
 26. exp evaluation/
 27. exp prospective study/
 28. (control\$ or prospectiv\$ or volunteer\$).tw.
 29. or/25-28
 30. 29 not 10
 31. 30 not (11 or 23)
 32. 11 or 24 or 31
 33. onchocerciasis/
 34. exp onchocerca/
 35. exp microfilaria/
 36. (onchocerc\$ or oncocerc\$).tw.
 37. (river adj2 blindness).tw.
 38. or/33-37
 39. ivermectin/
 40. ivermectin\$.tw.
 41. mectizan\$.tw.
 42. ivomec\$.tw.
 43. albendazole/
 44. albendazole\$.tw.
 45. levamisole/
 46. levamisole\$.tw.
 47. or/39-46
 48. 38 and 47
 49. 32 and 48

Appendix 4. metaRegister of Controlled Trials search strategy

onchocerciasis and ivermectin

Appendix 5. ClinicalTrials.gov search strategy

Onchocerciasis AND Ivermectin

Appendix 6. ICTRP search strategy

onchocerciasis and ivermectin

WHAT'S NEW

Date	Event	Description
16 July 2012	Review declared as stable	This review will no longer be updated as current medical practice has evolved beyond placebo comparisons. See ' Published notes ' for further information.

HISTORY

Protocol first published: Issue 3, 2000

Review first published: Issue 1, 2001

Date	Event	Description
11 June 2012	New search has been performed	Issue 8, 2012: Electronic searches were updated.
11 June 2012	New citation required but conclusions have not changed	Issue 8, 2012: No new studies were identified that met the inclusion criteria.

Date	Event	Description
12 August 2009	New search has been performed	Issue 4, 2009: Updated searches yielded no new trials. The background has been updated to include information on Loa loa infection (loaisis). Four studies are included instead of five as per the original published review as one report was of a subset of patients included in another trial.
30 October 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Conceiving the review: RW
Screening search results: HE, JE
Screening retrieved papers against inclusion criteria: HE, ES, JE
Appraising quality of papers: HE, ES, JE
Abstracting data from papers: HE,JE
Entering data into RevMan: HE, ES, JE
Analysis of data: HE, RW,JE
Writing the review: HE, RW,JE

DECLARATIONS OF INTEREST

Jennifer Evans worked on one of the included trials - [Abiose 1993](#).

SOURCES OF SUPPORT

Internal sources

- Institute of Ophthalmology, UK.

External sources

- British Council, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The main difference between the protocol and review is that we moved to assessing the risk of bias using The Cochrane Collaboration's tool for assessing risk of bias ([Higgins 2011](#)). In particular, we updated the methods for assessing the effect of heterogeneity, missing data and selective outcome bias as well as the language used to describe the authors judgment for each 'Risk of bias' domain.

NOTES

After consulting with the Cochrane Eyes and Vision editorial base, the review authors have decided to no longer update this review. The basis for this decision is in part due to ivermectin as the current standard of care which prohibits future placebo-controlled trials. Additional advances in the treatment and elimination of onchocerciasis now include combination treatments with a single dose of ivermectin plus daily doxycycline. Future Cochrane systematic reviews addressing additional therapies such as combination therapies for the treatment and elimination of onchocerciasis will add to the current evidence summarised here.

INDEX TERMS

Medical Subject Headings (MeSH)

Anthelmintics [*therapeutic use]; Ivermectin [*therapeutic use]; Onchocerciasis, Ocular [*drug therapy]; Randomized Controlled Trials as Topic; Vision Disorders [parasitology] [*prevention & control]

MeSH check words

Humans